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THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8865

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JUN 30 1975

Application for Research Grant
(Use extra pages as needed)

Date: 6/23/75

1. Principal Investigator (give title and degrees):

A. Sonia Buist, M.D.
Assistant Professor of Medicine and Physiology

2. Institution & address:

University of Oregon Health Sciences Center
School of Medicine
3181 S.W. Sam Jackson Park Road
Portland, Oregon 97201

3. Department(s) where research will be done or collaboration provided:

Department of Physiology

4. Short title of study:

The role of alpha$_1$ antitrypsin deficiency as a risk factor in the development of chronic airways obstruction.

5. Proposed starting date: January 1976

6. Estimated time to complete: 3 years

7. Brief description of specific research aims:

The specific aim of the proposed research is to examine the role of alpha$_1$ antitrypsin (α_1AT) deficiency as a risk factor in the development of chronic airway obstruction.

Cigarette smoking is the only factor known at present to bear a causal relationship to the development of chronic airway obstruction (1). Clearly, however, this is not a 1 to 1 relationship since all who smoke do not develop clinical or physiological evidence of impairment. Indeed, in a recent population survey carried out by the Collaborative Study on Smoking and Airways Obstruction* in which both spirometry and the closing volume test were used, the prevalence of physiologic impairment in smokers aged 25 to 54 from randomly selected populations in Portland, Montreal and Winnipeg, ranged between 15 and 25%. Furthermore, in this study, no dose response relationship was found between cigarettes and either closing volumes (closing volume (CV) expressed as a percent of vital capacity (VC) i.e. CV/VC, and closing capacity (CC) expressed as a percent of total lung capacity (TLC) i.e. CC/TLC) or the slope of the alveolar plateau of the single breath nitrogen test ($\Delta N_2/L$). (2) The conclusions drawn from this study were that factors other than smoking, such as environmental pollution, childhood infection, and/or genetic

* The Collaborative Study on Smoking and Airways Obstruction designates research carried out in Portland (A.S. Buist), Montreal (P.T. Macklem) and Winnipeg (R.M. Cherniack) under a contract from the National Heart and Lung Institute.

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7. (continued)

and biochemical factors play an important and perhaps synergistic role in the development of airway obstruction.

It has been well documented that homozygous α_1AT deficiency (P_i phenotype Z2) is strongly associated with the development of severe panlobular emphysema at an early age (3). However, it has also been demonstrated that some persons with homozygous α_1AT deficiency do not develop disease (4). The relationship between a homozygous deficiency of α_1AT and the development of disease is thus not entirely clear. The relationship between the heterozygous state (P_i phenotype MZ) and the development of disease is even more controversial. Some investigators have suggested that heterozygotes are no more at risk of developing emphysema than are persons with normal levels of α_1AT (5). Other investigators have put forward the opposite point of view (6) which has been supported by a recent study in which the results of lung function studies performed on 54 adults of P_i type MZ were compared to those in 69 adults with P_i type MM(7). In this study, the MZ adults had significantly inferior function as measured by arterial oxygen tension, lung elastic recoil, maximal expiratory flow and closing capacity. In addition, cigarette smoking and P_i type MZ interacted additively and caused greater reduction in function than either factor produced independently.

Unfortunately, most of the studies on α_1AT deficiency have had to use highly selected populations such as patients and relatives of patients attending outpatient clinics or hospital inpatients. This has led to difficulties in the interpretation of findings and some confusion as to the true role of α_1AT deficiency, both complete and partial, in the development of chronic airway obstruction. Exactly what this role is assumes considerable importance because the prevalence of α_1AT heterozygosity (P_i phenotype MZ) has been estimated at 30 per 1000 of the newborn population in the United Kingdom (8) and also because α_1AT deficiency is to date the only known model of a genetically inherited condition which leads to the development of chronic airway obstruction, with the exception of cystic fibrosis. The aim of the proposed research is to try to clarify the role of α_1AT deficiency as a risk factor in the development of chronic airway obstruction by establishing a cohort of P_i type MZ heterozygotes, and following the cohort prospectively over a period of years with repeated lung function tests.

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8. Brief statement of working hypothesis:

The hypotheses to be tested are that:

(i) MZ heterozygotes for α_1AT deficiency have impaired lung function as measured by a wide range of tests of lung mechanics.

(ii) The MZ heterozygote does not belong to the high risk category for the development of chronic airway obstruction unless there is some additive factor such as cigarette smoking, occupational exposure to pollutants or atopic history.

9. Details of experimental design and procedures (extra pages appended)

(i) Subjects:

Since 1971, neonatal screening for α_1AT deficiency has been carried out on cord blood samples from all newborns in Oregon. To date 22 infants with P_i type ZZ homozygous α_1AT deficiency have been detected and confirmed out of a total of 110,000 births, giving a gene frequency in Oregon of approximately 1 in 30 of the population. We propose to do family pedigrees on these infants and attempt to study all first degree relatives. Since the parents of the infants will mostly be young (in 20's and 30's), this will establish an excellent cohort for prospective study

(ii) Methods

(a) Spirometry:

Tests for the measurement of forced vital capacity (FVC), FEV_1 and $MMEF_{25-75\%}$ will be performed on all subjects using standardized spirometric methods as established for epidemiologic studies by the National Heart and Lung Institute (9). Tests will be performed on a Vitalograph wedge-type spirometer or Bennett Remac Pulmonary Function Testing Unit. Both instruments will be calibrated against a Collins Stead-Wells spirometer at regular intervals. Using the prediction equations of Morris et al.(10), an abnormal test value would be defined as a value which is > -2 SEE below the predicted value for age, sex and height.

(b) Single breath nitrogen test for measurement of closing volumes:

Closing volume, CC, TLC, RV and $\Delta N_2/L$ will be obtained from the SBNT for the measurement of closing volumes as standardized by the Collaborative Study on Smoking and Airways Obstruction (11). The equipment currently used for this test includes a rolling seal spirometer (Cardio Pulmonary Instruments), a nitrogen analyzer (Med-Science), XYY' Recorder (Hewlett Packard) and bag-in-box system.

(c) Lung mechanics:

Static pressure-volume (P-V) curves, and maximum expiratory flow-volume (MEFV) curves using air and an oxygen-helium (O_2-He) mixture for measurement of volume of isoflow (V_{isoV}) as described by

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9. (ii) (c) continued

Hutcheon et al. (12) will be carried out using the standardized procedure proposed by the Collaborative Study on Smoking and Airway Obstruction (13). The equipment used for studies of lung mechanics will include an Ohio 3000 constant volume body plethysmograph to be used as an integrated-flow plethysmograph as described by Leith and Mead (14).

(iii) Experimental Design

Initially a family pedigree of the proband will be drawn up. All first degree relatives of the proband over the age of 18 will be contacted and invited to participate in the study. Testing will consist of

(1) P_i phenotyping
(2) Respiratory system questionnaire (expanded NHLI questionnaire).
(3) Spirometric tests for measurement of FVC, FEV_1, $MMEF_{25-75\%}$.
(4) Single breath N_2 test for measurement of CV/VC, CC/TLC, $\Delta N_2/L$, TLC and RV.
(5) Lung mechanics studies for measurement of static P-V curves, V iso $\dot{V}$, flow at 50% VC ($\dot{V}_{max50}$) and 25% VC ($\dot{V}_{max\ 25}$).

After the initial test occasion, subjects will be asked to return for repeat testing probably at 2 year intervals. It is our intention to make this a long term prospective study. Controls matched for age, sex and smoking habits will be drawn from a long term prospect study, currently in progress, of a randomly selected population of non-smokers, smokers and ex-smokers living in Oregon. This cohort was first studied in 1974.

Data will be analyzed to look for differences in initial lung function between MZ/and MM subjects controls and for differences in the time course of change of the various tests of lung function between the different groups. We plan to follow the control group until 1980, (6 years total). It would be realistic to contemplate following the α_1AT cohort for a similar length of time in order to provide sound longitudinal data from which valid conclusions can be drawn about the role of α_1AT deficiency as a risk factor in the development of chronic airway obstruction.

SIGNIFICANCE

The important contribution that this study can make that is not readily available from other groups studying α_1AT deficiency is that we have been able to obtain an unselected population of homozygotes (P_i type ZZ) for study, i.e. a population which is truly representative of the frequency of α_1AT deficiency in Oregon. This has been made possible because all newborns in Oregon since 1971 have been tested, thereby giving access to a large population of heterozygotes which has not been selected on the basis of symptomatology or disease, or because the subjects were attending an outpatient clinic. In this way, an accurate assessment of the lung function of heterozygotes can be obtained and the role of the α_1AT heterozygous state in the development of chronic airways obstruction can be more clearly defined.

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REFERENCES

1. The health consequences of smoking. A report of the Surgeon General: 1974. DHEW

2. Buist, A.S., Macklem, P.T. and Cherniack, R.M.
Relationship between smoking and single breath nitrogen washout in Portland, Oregon, Winnipeg, Manitoba and Montreal, Quebec. To be presented at International Union Against Tuberculosis Meeting, Mexico City, Sept. 1975.

3. Guenter, C.A., Welch, M.H. and Hammarsten, J.F.
Alpha-1 antitrypsin deficiency and pulmonary emphysema. Annual Review of Medicine 22, 283, 1971.

4. Welch, M.H., Reinecke, M.E., Hammarsten, J.F. and Guenter, C.A.
Antitrypsin deficiency in pulmonary disease: The significance of intermediate levels. Ann. Intern. Med. 71, 533, 1969.

5. Mittman, C. Summary of Symposium on Pulmonary Emphysema and Proteolysis.
American Rev. Resp. Dis. 105, 431, 1972.

6. Lieberman, J.
Heterozygous and homozygous alpha$_1$-antitrypsin deficiency in patients with pulmonary emphysema.
New Engl. J. Med. 281, 279, 1969.

7. Cooper, D.M., Hoeppner, V., Cox, D. Zamel, N., Bryan, A.C., and Levison, H.
Lung function in alpha$_1$-antitrypsin heterozygotes (Pi type MZ).
American Review of Respiratory Dis. 110, 708, 1974.

8. Cook, P.J.L.
Genetic aspects of the Pi system. Postgrad. Med. J. 50, 362, 1974.

9. Recommended Standardized Procedures for NHLI Lung Program Epidemiology Studies, NHLI, 1971.

10. Morris, J.F., Koski, W.A. and Johnson, L.C.
Spirometric standards for healthy nonsmoking adults. Amer. Rev. Resp. Dis. 103, 57, 1971.

11. Suggested standardized procedures for closing volume determinations (Nitrogen Method), distributed by NHLI, 1973.

12. Hutcheon, M., Griffin, P., Levison, H., and Zamel, N.:
Volume of isoflow Amer. Rev. Resp. Dis. 110, 458, 1974.

13. Macklem, P.T.,
Procedures for standardized measurements of lung mechanics.
Distributed by NHLI, Nov. 1974.

14. Leith, D.E. and Mead, J.
Principles of body plethysmography available from National Heart and Lung Institute, Nov. 1974.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The facilities currently in use include a laboratory (725 sq. ft.), equipped for general research in respiratory physiology, an office (130 sq. ft.) occupied by Dr. Buist. All of these facilities are located in the Department of Physiology.

The major items of permanent equipment on hand include:

1. Ohio 3000 Body Plethysmograph System, modified to be used as an integrated flow plethysmograph.
2. Hewlett-Packard XYY' Recorder and Houston Instrument XY Recorder.
3. CPI 220 Rolling Seal Spirometer.
4. Med Science N_2 Analyzer.
5. Hewlett-Packard Programmable Computer 9810 and Plotter (shared).
6. Brush 2 Channel Recorder
7. Stead-Wells Spirometer.

Antitrypsin deficiency in pulmonary disease. The significance of intermediate levels. Ann. Intern. Med. 71, 533, 1969.

Heterozygous and homozygous alpha$_1$-antitrypsin deficiency in patients with pulmonary emphysema

11. Additional facilities required:

Rotameter (Fisher-Porter) for calibrating body plethysmograph for air and helium.

8. Cook, P.J.L.

NHLI, 1971.

12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

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12. Biographical Sketch

Aline Sonia Buist, M.B., Ch.B., M.D.
Assistant Professor of Medicine and Physiology

PERSONAL:
Birthdate: REDACTED
Married: REDACTED
Children: R

EDUCATION:

R University of St. Andrews Medical School, M.B., Ch.B.
R Residency in General Practice and Internal Medicine, University of Colorado Medical School
R Fellowship in Pediatric Chest Disease, University of Oregon Medical School
R Bellinger Fellowship in Clinical Pulmonary Disease (part time)
R Fellowship in Pulmonary Physiology, University of Oregon Medical School

EXPERIENCE:

Teaching

1970-1972 Clinical Instructor in Medicine, University of Oregon Medical School
1970-1972 Clinical Research Associate, Dept. of Physiology, University of Oregon Medical School
1972-pres. Assistant Professor of Medicine, Division of Chest Diseases, University of Oregon Medical School
1975-pres. Assistant Professor of Medicine, Dept. of Physiology, University of Oregon Medical School

Extramural Boards, Committees, Consults., etc.

1970-1972 Medical Director, Emphysema Screening and Research Center, Portland, Oregon
1974-pres. NIH Study Section for Young Investigators Pulmonary Research Awards
Pulmonary Academic Awards Committee, National Heart Lung Institute
Committee of the Structure and Function Assembly, American Thoracic Society
1975-pres. Member of Cardiovascular and Respiratory Study Section, National Heart and Lung Institute

HONORS

M.D. with commendation, University of Dundee, 1973

SOCIETY MEMBERSHIPS

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13. PUBLICATIONS:

1. Buist, A.S. and Ross, B.B. Predicted values for closing volumes using a modified single breath nitrogen test. Amer. Rev. Resp. Dis. 107: 744, 1973.

2. Buist, A.S., Van Fleet, D.L., and Ross, B.B. A comparison of spirometric tests and the measurement of closing volumes in an Emphysema Screening Center. Amer. Rev. Resp. Dis. 107: 735, 1973.

3. Buist, A.S. Early detection of airways obstruction by the closing volume technique. Chest. 64: 495, 1973.

4. Buist, A.S. and B.B. Ross. Quantitative analysis of the alveolar plateau in early airway obstruction. Amer. Rev. Resp. Dis. 108: 1078, 1973.

5. Buist, A.S. Current Concepts: The single breath nitrogen test. New Engl. J. of Med. In press.

1970-1972 Medical Director, Emphysema Screening and Research Center,

Research Awards

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Budget Justification

Salaries

Two half-time salaries are requested -- for a research associate with considerable experience with the sophisticated electronics entailed in body plethysmography (Mr. B.E. Adams) and one for a research assistant to track down the subjects, do family pedigrees, spirometry and reduction of data.

No salaries are requested for Dr. Buist and Dr. Sexton. Dr. Buist currently holds a Research Career Development Award from the National Heart and Lung Institute and Dr. Sexton holds a Postdoctoral Statistical Fellowship (NIH Grant GMS 01736).

Equipment

A rotameter is requested for calibrating the body plethysmograph for air and helium.

Years 2 and 3

A 10% increase is requested for all categories of the budget with the exception of the equipment category. $500 for years 2 and 3 are requested for the purchase or replacement of minor items of equipment. e.g. transducer for body plethysmograph, needle valve for N_2 analyzer, new pneumotach lead, etc.

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14. First year budget:

A. Salaries (give names or state "to be recruited")		% time	Amount
Professional (give % time of investigator(s) even if no salary requested)			
A.S. Buist	Principal Investigator	25%	REDACTED
B.E. Adams	Research Associate	50%	
G. Sexton	Statistical Postdoctoral Fellow	20%	
Technical			
To be recruited	Research Assistant	50%	$4,500
Payroll assessment 15% includes FICA, Pers, SIAC, etc. = $2,025			$2,025
		Sub-Total for A	$15,525

B. Consumable supplies (by major categories)

Supplies for spirometry and single breath N_2 test, (O_2, calibrating gases, mouthpieces, etc.)	500
Supplies for body plethysmography (O_2, helium, esophageal balloons, mouthpieces, polaroid film, topical anesthesia, etc.)	500
Secretarial supplies, sterilizing materials, recording paper, etc.	500
Sub-Total for B	$ 1,500

C. Other expenses (itemize)

Computer costs (keypunching @ $6/hr, programming @ $9/hr and computer time @ $300/hr)	1,000
Service and repair of equipment	1,000
Postage, telephone, xerox	250
Sub-Total for C	$ 2,250
Running Total of A + B + C	$19,275

D. Permanent equipment (itemize)

Rotameter	395
Sub-Total for D	$ 395
E	$ 2,891
Total request	$22,561

E. Indirect costs (15% of A+B+C)

15. Estimated future requirements:

	Salaries	Consumable Suppli	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	17,078	1,650	2,475	500	3,180	24,883
Year 3	18,785	1,815	2,723	500	3,498	27,321

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16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Smoking and Chronic Airways Obstruction	NIH-NHLI Contract N01-HR3-2900	$209,472	September 1972 - August 1975
Research Career Development Award	NIH-NHLI 1 K04 HL00115	$ 25,000	February 1975 - January 1976

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Natural history of chronic airways obstruction*	NIH-NHLI	$347,275	September 1975 - August 1980
Smoking and Chronic Airways Obstruction*	NIH-NHLI Renewal of Contract N01-HR3-2900	$354,938	September 1975 - August 1979

* If awarded the contract, the grant application will be withdrawn.

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name A. Sonia Buist

Signature [redacted] Date 6/23/75

Telephone ___ Area Code ___ Number ___ Extension ___

Checks payable to

University of Oregon Health Sciences Center

Mailing address for checks

3181 S.W. Sam Jackson Park Road

Portland, Oregon 97201

Responsible officer of institution

Typed Name Lewis W. Bluemle, Jr., M.D.

Title President

Signature [redacted] Date 6-25-75

Telephone ___ Area Code ___ Number ___ Extension ___

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